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10/821,657	04/08/2004	H. Garrett Wada	100/18002	8775

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CALIPER LIFE SCIENCES, INC.
605 FAIRCHILD DRIVE
MOUNTAIN VIEW, CA 94043-2234

EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

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10/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,657	WADA ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-44,51,53 and 55-100* is/are pending in the application.

4a) Of the above claim(s) *5,7,80 and 82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 8-29, 31-44, 51, 53, 55-79, 81, and 83-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/05/2007 has been entered.

2. This action is in response to the papers filed 7/05/2007. Currently, Claims 1-29, 31-44, 51, 53, and 55-100 are pending. Claims 30, 45-50, 52, and 54 have been canceled. Claims 5, 7, 80, 82 are withdrawn as being drawn to a nonelected invention.

3. The following rejections for Claims 1-4, 6, 8-29, 31-44, 51, 53, 55-79, 81, and 83-100 are newly applied as necessitated by amendment. Response to arguments follows.

4. This action is NONFINAL.

Withdrawn Rejections

5. The rejection of Claims 37-40 and 95-97 made under 35 USC 112/2nd paragraph in section 6 of the previous office action is moot in view of the cancellation of the claims.

Election/Restrictions

6. The reply asserts that Claims 5, 7, 80, 82 are withdrawn as being drawn to a nonelected species however upon the allowance of a generic claim the species will be rejoined (p. 20 of reply). The examiner acknowledges that Claims 5, 7, 80, and 82 are species claims which will be rejoined upon the allowance of a generic claim.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-3, 6, 9-29, 33, 35-44, 51-55, 59-65, 67, 68-78, 81, 83, 85-86, 90, and 92-100 rejected under 35 U.S.C. 103(a) as being unpatentable over Kawabata et al. (EP 1376126A1 3/04/2002) as evidenced by Walston et al. (US Patent Application Publication 2001/0055591 December 27, 2001) in view of Krylov et al. (Anal Chem 2000 Vol. 72 p. 111R).

CLAIM 1 is an independent Claim.

With regard to Claim 1, Kawabata et al. teaches a method of measuring a target (detecting an analyte) (Abstract). Kawabata et al. teaches a target substance (analyte) is reacted with an affinity molecule forming a complex (p. 1 paragraph 0008). Kawabata et al. teaches the separation of the complex from nucleic acid chain-binding affinity substances not involved in the formation of the complex (separation of the complex and unbound affinity molecule) (p. 13 paragraph 73). Kawabata et al. teaches adding heparin (charged polymer) to the solution of nucleic acid chain-binding affinity substances in the separation method (p. 23 paragraphs 144-145). Walston et al. defines heparin is a polysaccharide with a strong negative charge (p. 2 paragraph 0016). Kawabata et al. teaches separating the complex using capillary electrophoresis with a channel diameter preferably 1 to 200 microns (p. 12 paragraph 58). Kawabata et al. teaches using heparin to block nucleases to inhibit digestion therefore reducing the interference from Dnase and Rnase (p. 23 paragraphs 144-145). Kawabata et al. teaches a method for measuring (detecting) a target separated by complexing with a nucleic acid chain-binding affinity substance (abstract).

Claims 2-3, 6, 9-13, 22, 27, 35-36, 43-44 depend from Claim 1

With regard to Claims 2-3, and 6, Kawabata et al. teaches using heparin (p. 23 paragraphs 144-145). Walston et al. teaches heparin is a polysaccharide with a strong negative charge (p. 2 paragraph 0016).

With regard to Claims 9 and 22, Kawabata et al. teaches a nucleic acid chain affinity substance is labeled with a marker (Figure 2). With regard to Claims 11, 12, and 13, Kawabata et al. teaches the binding of "protein" and "peptide chain"; "antigen" and "antibody"; "sugar chain" and "lectin"; "enzyme" and "inhibitor"; and "receptor" and "ligand" (p. 6 paragraph 20).

With regard to Claim 10, Kawabata et al. teaches a nucleic acid chain (charge carrier molecule) attached to an affinity substance attached to a target (analyte) (Figure2). Claims 16-18 defines nucleic acids as having a negative charge. Kawabata et al. teaches the addition of the charged substance improves separation ability (p. 2-3 paragraph 9).

With regard to Claim 27, Kawabata et al. teaches the use of fluorescent dyes and radioactive tracers (p. 8 paragraph 26).

With regard to Claim 35, Kawabata et al. teaches the diameter of the capillary channel (cross sectional microscale dimension) of between 1 to 200 microns (p. 12 paragraph 58).

Claims 14-21, 23-26, 28-29, 33, 37, 38, 94-96 depend from Claim 10

With regard to Claim 14, Kawabata et al. teaches the charged carrier molecule is a nucleic acid chain (anionic) (p. 3-4 paragraph 6). With regard to Claim 15, the

charged carrier molecule is a nucleic acid chain (negative charge) and the charged polymer is a heparin (negative charge).

With regard to Claims 16-17, Kawabata et al. teaches the charged carrier is a nucleic acid chain (nucleotide chain, DNA) (p. 3-4 paragraph 6).

With regard to Claims 18, Kawabata et al. teaches the charged carrier is a nucleic acid chain (nucleotide chain, DNA) (p. 3-4 paragraph 6). Kawabata et al. teaches the nucleic acid chain used may be prepared by chemical synthesis (synthetic) (p. 6 paragraph 15). With regard to Claims 19-21, Kawabata et al. teaches a method of labeling the nucleic acid with a linker, such as, Sulfo-SMPB (sulfosuccinimidyl) (succinimide group) (p. 7 paragraph 22 and p. 9 paragraph 32).

With regard to Claims 23-24, Kawabata et al teaches a nucleic acid chain attached to an affinity substance and labeled with a marker (Figure 2). The conjugate is the nucleic acid chain attached to the affinity substance. With regard to Claim 25, Kawabata et al. teaches the nucleic acid chain is labeled (Figure 2).

Claim 26 is drawn to an affinity molecule in the conjugate, which is labeled by a detectable marker. The claim is not limited to a label, which is directly connected to the affinity or directly connected with a linker to an affinity. Therefore, since in the conjugate the nucleic acid is directly attached to the affinity and the nucleic acid is labeled the affinity would be labeled. Kawabata et al. teaches a method using an Alexa488-labeled anti-AFP antibody Fab' fragment (p. 24 p. 152).

With regard to Claim 28, Kawabata et al. teaches separating the complex using capillary electrophoresis (p. 12 paragraph 58). With regard to Claim 29, Kawabata et al.

teaches the separation media can be comprised of polyethylene glycol, polyacrylamide, polyethylene oxide, or polyvinylpyrrolidone (p. 12, paragraph 59).

With regard to Claim 33, Kawabata et al. teaches using heparin in a solution containing the target (p. 23 paragraphs 144-145). Walston et al. teaches heparin is a polysaccharide with a strong negative charge (p. 3 paragraph 5).

With regard to Claim 36, Kawabata et al. teaches a target substance (analyte) is reacted with an affinity molecule forming a complex (p. 2 paragraph 8). Kawabata et al. teaches the separation of the complex from nucleic acid chain-binding affinity substances not involved in the formation of the complex (separation of the complex and unbound affinity molecule) (p. 13 paragraph 74). Kawabata et al. teaches a method of measuring a target (detecting an analyte) (Abstract). With regard to Claim 94, Kawabata et al. teaches at least two affinity molecules which bind to the target (analyte) at different sites (Figure 4).

With regard to Claim 43, Kawabata et al. teaches targets comprising serum, plasma, urine, feces, and environmental samples (p. 11 paragraph 49). With regard to Claim 44, Kawabata et al. teaches a target comprising AFP, FSH, TSH, LH, HIV, CA10-19, CA125, PSA, or T4 (p. 5 paragraph 56).

Claim 37 has every limitation of Claim 10, but also includes the limitation that two or more conjugates are used wherein each affinity molecule is capable of binding the analyte at a different site. Kawabata et al. teaches at least two affinity molecules (in a complex) which bind to the target (analyte) at different sites (Figure 4). With regard to

Claim 95, Kawabata et al. teaches at least two affinity molecules which bind to the target (analyte) at different sites (Figure 4).

Claim 38 has every limitation of Claim 10, but also the limitation that the affinity molecule and the affinity molecule in the conjugate have a property capable of binding to the analyte at a different site on the analyte form every other affinity molecule. Kawabata et al. teaches a method in which the nucleic acid (charged carrier molecule), affinity molecules, and analytes are in a solution together (Figure 2). Kawabata et al. teaches at least two affinity molecules (in a complex) which bind to the target (analyte) at different sites (Figure 4). With regard to Claim 96, Kawabata et al. teaches at least two affinity molecules which bind to the target (analyte) at different sites (Figure 4).

Claim 39 is an independent Claim and Claims 40-41, and 97-99 depend from Claim 39

With regard to Claims 39-41 and 97-99, Kawabata teaches a method in which an analyte, affinity, and a charge polymer form a complex which is labeled (first complex) (Figure 6). The claim does not limit how the analyte is labeled so therefore a conjugate comprising the analyte, affinity, and a labeled charged polymer would encompass the claims. Kawabata et al. teaches 2 or more of these complexes can be made (Figure 6). Kawabata et al. teaches separating the sample (Figure 6). Kawabata et al. teaches 2 or more affinity molecules can be used (Figure 6). Kawabata et al. teaches measuring and determining the amount of analyte in the sample (Abstract). Kawabata et al. teaches at least two affinity molecules which bind to the target (analyte) at different sites (Figure 4).

Claim 42 is an independent Claim and Claims 100 depend from Claim 42

With regard to Claim 42, it is unclear in the claim which combination is actually needed in the first complex. With regard to the first complex, Kawabata et al. teaches contacting the sample with a complex of analyte, affinity, and detectable marker (figure 2). Since the analyte is labeled in this complex because of the attachment of the labeled charged molecule it is unclear what the difference it between the first and second complex. Kawabata et al, teaches 2 or more types of targets can be labeled (forming 2 or more complexes) and separated (Figure 6). Further Kawabata et al. teaches that two ore more affinity molecules may be used in the separation (Figure 6). With regard to Claim 100, Kawabata et al. teaches at least two affinity molecules which bind to the target (analyte) at different sites (Figure 4).

Claim 51 is an independent Claim.

With regard to Claim 51, Kawabata et al. teaches contacting a sample, with an affinity attached to a nucleic acid chain, which is labeled (Figure 2). Kawabata et al. teaches separating the complex using capillary electrophoresis (p. 12 paragraph 58). Kawabata et al. teaches a method of capillary chip electrophoresis comprising adding a buffer and sample to a sample reservoir, applying voltage and migrating the sample through a capillary wherein the sample which goes completely through the first capillary is introduced into a capillary for separation (p. 12 paragraph 56 and Figure 7). For the first capillary, the sample is concentrated because only the sample that goes through

the entire first capillary is introduced into the capillary for separation, therefore, the first capillary is a concentration channel. Kawabata et al. teaches the capillary used is 100 micron or less (p. 11-12 paragraph 54). Kawabata et al. teaches a nucleic acid chain (charge carrier molecule) attached to an affinity substance attached to a target (analyte) (Figure2). Kawabata et al. teaches the addition of the charged substance improves separation ability (p. 2-3 paragraph 9).

Claims 52-55, 59-65, 67, 68-78, 81, 83, 85-86, 90, and 92 depend from Claim 51

With regard to Claim 52, the specification does not define noise constituent. Kawabata et al. teaches a separation of the conjugate from the nucleic acid chain-binding affinity substance-marker not involved in the formation of the complex. Therefore in separating the conjugate not in the complex from the complex the concentration of the noise constituent is lowered. The noise constituent is anything that is not in the complex.

With regard to Claim 53, Kawabata et al. teaches the capillary used is 100 micron or less (p. 11-12 paragraph 54). Kawabata et al. teaches a method of capillary chip electrophoresis comprising adding a buffer and sample to a sample reservoir, applying voltage and migrating the sample through a capillary wherein the sample which goes completely through the first capillary is introduced into a capillary for separation (p. 12 paragraph 56 and Figure 7). Therefore the complex goes through a concentration channel (first capillary) and then to the separation capillary in a solution stopping at a reservoir between the two capillaries (microchannel fluidically).

With regard to Claim 54, it is unclear how the buffer affects the sample. Kawabata et al. teaches buffers for use in migration including tris, phosphate, Veronal, borate, Good's, SSC, TBE and TAE (p. 12 paragraph 63).

With regard to Claim 55, Kawabata et al. teaches that retention time (electrophoretic mobility) was different between the labeled conjugate and the antibody alone (noise constituents) (p. 27 paragraph 170). Kawabata et al. teaches that separation ability is improved with the use of a charged substance (p. 2-3 paragraph 9).

With regard to Claims 59-61, Kawabata et al. teaches the charged carrier is a nucleic acid chain (nucleotide chain, DNA) (p. 3-4 paragraph 6). With regard to Claim 62, Kawabata et al. teaches the nucleic acid chain used may be prepared by chemical synthesis (synthetic) (p. 6 paragraph 15). With regard to Claims 63-65, Kawabata et al. teaches a method of labeling the nucleic acid with a linker, such as, Sulfo-SMPB (sulfosuccinimidyl) (succinimide group) (p. 7 paragraph 22 and p. 9 paragraph 32).

With regard to Claim 67, Kawabata et al. teaches a nucleic acid chain (charge carrier molecule) attached to an affinity substance attached to a target (analyte) (Figure2). With regard to Claims 68-69, Kawabata et al. teaches the binding of "protein" and "peptide chain"(protein: protein interaction); "antigen" and "antibody"; "sugar chain" and "lectin"; "enzyme" and "inhibitor"; and "receptor" and "ligand" (p. 6 paragraph 20). With regard to Claim 70, Kawabata et al. teaches the affinity molecule can be FAB, $F(ab')_2$ (p. 6 paragraph 21).

With regard to Claim 71, Kawabata et al teaches a nucleic acid chain attached to an affinity substance and labeled with a marker (Figure 2). The conjugate is the nucleic acid chain attached to the affinity substance.

Claim 74 is drawn to an affinity molecule in the conjugate, which is labeled by a detectable marker. The claim is not limited to a label, which is directly connected to the affinity or directly connected with a linker to an affinity. Therefore, since in the conjugate the nucleic acid is directly attached to the affinity and the nucleic acid is labeled the affinity would be labeled. Kawabata et al. teaches a method using an Alexa488-labeled anti-AFP antibody Fab' fragment (p. 24 paragraph 152).

With regard to Claims 72-73, Kawabata et al. teaches an affinity attached to a nucleic acid chain, which is labeled (Figure 2). With regard to Claim 75, Kawabata et al. teaches the use of fluorescent dyes and radioactive tracers (p. 8 paragraph 26).

With regard to Claim 76, Kawabata et al. teaches adding heparin (charged polymer) to the solution of nucleic acid chain-binding affinity substances (p. 23 paragraphs 144-145). Kawabata et al. teaches a method of capillary chip electrophoresis comprising adding a buffer and sample to a sample reservoir, applying voltage and migrating the sample through a capillary wherein the sample which goes completely through the first capillary is introduced into a capillary for separation (p. 12 paragraph 56 and Figure 7). For the first capillary, the sample is concentrated because only the sample that goes through the entire first capillary is introduced into the capillary for separation, therefore, the first capillary is a concentration channel. Therefore

Kawabata et al. teaches a solution with a charged polymer added to a concentration channel.

With regard to Claim 77-78, Kawabata et al. teaches using heparin in a solution containing the target (p. 23 paragraphs 144-145). Walston et al. teaches heparin is a polysaccharide with a strong negative charge (p. 3 paragraph 6).

With regard to Claim 81, Kawabata et al. teaches a nucleic acid chain (charge carrier molecule) attached to an affinity substance attached to a target (analyte) (Figure2).

With regard to Claim 83, Kawabata et al. teaches a nucleic acid chain (charge carrier molecule) and heparin (charged polymer) (Figure 2, p. 23 paragraphs 144-145). Both the nucleic acid chain and heparin are negatively charged.

With regard to Claims 85-86, Kawabata et al. teaches a method of capillary chip electrophoresis comprising adding a buffer and sample to a sample reservoir, applying voltage and migrating the sample through a capillary wherein the sample which goes completely through the first capillary is introduced into a capillary for separation (p. 12 paragraph 56 and Figure 7). Kawabata et al. teaches the capillary is filled with a filler such as, polyethylene glycol, polyethylene oxide, polyvinylpyrroliodone, and polyacrylamide (p. 12 paragraph 59). With regard to Claim 90, Kawabata et al. teaches a nuclease inhibitor such as heparin is added to the sample solution (p. 23 paragraph 144-145). Walston et al. teaches heparin is a polysaccharide with a strong negative charge (p. 3 paragraph 6).

With regard to Claim 92, Kawabata et al. teaches the capillary used is 100 micron or less (p. 11-12 paragraph 54).

Claim 93 is an independent Claim

With regard to Claim 93, Kawabata et al. teaches a method of capillary chip electrophoresis comprising adding a buffer and sample to a sample reservoir, applying voltage and migrating the sample through a capillary wherein the sample which goes completely through the first capillary is introduced into a capillary for separation (p. 12 paragraph 56 and Figure 7). Kawabata et al. teaches a method of measuring a target (detecting an analyte) (Abstract). Kawabata et al. teaches a target substance (analyte) is reacted with an affinity molecule forming a complex (p. 2 paragraph 8). Kawabata et al. teaches the separation of the complex from nucleic acid chain-binding affinity substances not involved in the formation of the complex (separation of the complex and unbound affinity molecule) (p. 13, paragraph 74). Kawabata et al. teaches adding heparin (charged polymer) to the solution of nucleic acid chain-binding affinity substances in the separation method (p. 23 paragraphs 144-145). Kawabata et al. teaches adding heparin (charged polymer) to the solution of nucleic acid chain-binding affinity substances in the separation method (p. 23 paragraphs 144-145). Walston et al. teaches heparin is a polysaccharide with a strong negative charge (p. 3 paragraph 5). Kawabata et al. teaches using heparin to block nucleases to inhibit digestion therefore reducing the interference from Dnase and Rnase (p. 23 paragraphs 144-145). Kawabata et al. teaches a method for measuring (detecting) a target separated by complexing with a nucleic acid chain-binding affinity substance (abstract).

However, Kawabata et al. does not teach filling a separation channel with a separation media and a charged polymer before separation.

With regard to Claims 1, 39, 42, 51 and 93, Krylov et al. teaches a method of affinity capillary electrophoresis that exploits the difference in electrophoretic mobilities between a free analyte and an analyte-ligand complex (p. 122R 1st column last paragraph). Krylov et al. teaches immobilizing heparin on the capillary wall of the separation chamber (p. 122R 2nd column 1st full paragraph).

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the capillary electrophoresis method of Kawabata et al. to include heparin in the separation chamber as taught by Krylov et al. The ordinary artisan would have been motivated to modify the capillary electrophoresis method of Kawabata et al. to include heparin in the separation chamber as taught by Krylov et al., because Krylov et al. teaches that dissociation constants of heparin complexes affect the migration time of the affinity and affinity-ligand complexes (p. 122R 2nd column 1st full paragraph). Krylov et al. teaches that immobilizing the heparin increases the migration time (p. 122R 2nd column 1st full paragraph). The ordinary artisan would be motivated to immobilize the heparin in the capillary solution in order to increase the migration time allowing for the separation of affinity and affinity-ligand complexes to become more distinct.

Response to Arguments

The reply traverses the rejection. The reply asserts that Kawabata et al. do not teach a separation channel in a microfluidic device filled with separation media and a charged polymer and performing a separation step (p. 22 paragraph 1, 2, 3). This argument has been thoroughly considered but has not been found persuasive. Though Kawabata et al. does not teach adding heparin to the separation media prior to the separation step, Krylov et al. teaches addition of the heparin to the capillary tube prior to separation in order to increase the migration time allow which would allow for a more distinct separation between the affinity and the affinity-ligand complexes.

9. Claims 4, 8, 79, and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawabata et al. (EP 1376126A1 3/04/2002) as evidenced by Walston et al. (US Patent Application Publication 2001/0055591 December 27, 2001) in view of Krylov et al. (Anal Chem 2000 Vol. 72 p. 111R) as applied to Claims 1-3, 6, 9-29, 33, 35-44, 51-55, 59-65, 67, 68-78, 81, 83, 85-86, 90, and 92-100 in the rejection above and in view of Bickel et al. (Proceedings of Natl. Acad. Sci. November 1992 Vol. 89 p. 10001).

Kawabata et al. teaches a method of measuring a target (detecting an analyte) (Abstract). Kawabata et al. teaches a target substance (analyte) is reacted with an affinity molecule forming a complex (p. 1 paragraph 0008). Kawabata et al. teaches the separation of the complex from nucleic acid chain-binding affinity substances not involved in the formation of the complex (separation of the complex and unbound affinity molecule) (p. 13 paragraph 73). Kawabata et al. teaches adding heparin (charged

polymer) to the solution of nucleic acid chain-binding affinity substances in the separation method (p. 23 paragraphs 144-145). Kawabata et al. teaches separating the complex using capillary electrophoresis with a channel diameter preferably 1 to 200 microns (p. 12 paragraph 58). Kawabata et al. teaches a method for measuring (detecting) a target separated by complexing with a nucleic acid chain-binding affinity substance (abstract). Krylov et al. teaches immobilizing heparin on the capillary wall of the separation chamber (p. 122R 2nd column 1st full paragraph).

Kawabata et al. and Krylov et al., however, are silent with regard to if the heparin is heparin sulfate.

Bickel et al. teaches a method of detecting specific RNA-protein complexes on a polyacrylamide gel with inhibitors (Figure 1 paragraph p. 10002). With regard to Claims 4, 8, 79, and 84 Bickel et al. teaches using heparin sulfate as a nonspecific competitor in an SDS gel (p. 10003 1st column 1st paragraph and Figure 3).

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the capillary electrophoresis method of Kawabata et al. and Krylov et al. to include heparin sulfate as a nonspecific competitor as taught by Bickel et al. The ordinary artisan would have been motivated to modify the capillary electrophoresis method of Kawabata et al. and Krylov et al. to include heparin sulfate as a nonspecific competitor as taught by Bickel et al., because Bickel et al. teaches the addition of heparin sulfate made the complex migrate more rapidly and simplified the pattern of proteins on the SDS gels (p. 1005 1st paragraph). Bickel et al. teaches heparin increases the intensity of faint bands (p. 1005 1st paragraph).

Response to Arguments

The reply traverses the rejection. The reply asserts the art presented in the rejection do not teach a separation channel in a microfluidic device filled with separation media and a charged polymer. This argument has been thoroughly considered but has not been found persuasive. As discussed above in the rejection of Kawabata et al. and Krylov et al. the arguments and amendments have not overcome the art of record.

10. Claims 31-32 and 88-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawabata et al. (EP 1376126A1 3/04/2002) as evidenced by Walston et al. (US Patent Application Publication 2001/0055591 December 27, 2001) in view of Krylov et al. (Anal Chem 2000 Vol. 72 p. 111R) as applied to Claims 1-3, 6, 9-29, 33, 35-44, 51-55, 59-65, 67, 68-78, 81, 83, 85-86, 90, and 92-100 in the rejection above in further view of Stathakis et al. (Journal of Chromatography A 1998 Vol. 817 p. 227).

Kawabata et al. teaches a method of measuring a target (detecting an analyte) (Abstract). Kawabata et al. teaches a target substance (analyte) is reacted with an affinity molecule forming a complex (p. 1 paragraph 0008). Kawabata et al. teaches the separation of the complex from nucleic acid chain-binding affinity substances not involved in the formation of the complex (separation of the complex and unbound affinity molecule) (p. 13 paragraph 73). Kawabata et al. teaches adding heparin (charged polymer) to the solution of nucleic acid chain-binding affinity substances in the

separation method (p. 23 paragraphs 144-145). Kawabata et al. teaches separating the complex using capillary electrophoresis with a channel diameter preferably 1 to 200 microns (p. 12 paragraph 58). Kawabata et al. teaches a method for measuring (detecting) a target separated by complexing with a nucleic acid chain-binding affinity substance (abstract). Krylov et al. teaches immobilizing heparin on the capillary wall of the separation chamber (p. 122R 2nd column 1st full paragraph).

Therefore Kawabata et al. and Krylov et al. teaches a charged polymer in a separation media because Krylov et al. teaches immobilizing heparin to the capillary wall of the separation chamber, however, Kawabata et al. and Krylov et al. do not teach the concentration of charged polymer in a separation media.

With regard to Claims 30 and 87, Stathakis et al. teaches a coating on the capillary electrophoresis silica fuse glass, which contains dextran sulfate or polyvinyl suphonic acid (PVS) (abstract and p. 230 2nd column Section 3.3). With regard to Claims 31-32 and 88-89, Stathakis et al. teaches a method using 0.001-0.1% dextran or 0.001-1% PVS (p. 230 last paragraph).

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the capillary electrophoresis method of Kawabata et al. and Krylov et al. to include charged polymers in a particular concentration in the separation media as taught by Stathakis et al. The ordinary artisan would have been motivated to modify the capillary electrophoresis method of Kawabata et al. and Krylov et al. to include charged polymers in separation media as taught by Stathakis et al., because Stathakis et al. teaches polymers incorporated in the

separation buffer can improve migration time reproducibility (p. 229 2nd column 1st sentence).

Response to Arguments

The reply traverses the rejection. The reply asserts the art presented in the rejection do not teach a separation channel in a microfluidic device filled with separation media and a charged polymer. This argument has been thoroughly considered but has not been found persuasive. As discussed above in the rejection of Kawabata et al. and Krylov et al. the arguments and amendments have not overcome the art of record.

11. Claims 34 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawabata et al. (EP 1376126A1 3/04/2002) as evidenced by Walston et al. (US Patent Application Publication 2001/0055591 December 27, 2001) in view of Krylov et al. (Anal Chem 2000 Vol. 72 p. 111R) as applied to Claims 1-3, 6, 9-29, 33, 35-44, 51-55, 59-65, 67, 68-78, 81, 83, 85-86, 90, and 92-100 in the rejection above in further view of Stalcup et al. (Analytical Chemistry 1994 Vol. 66 p. 3054).

Kawabata et al. teaches a method of measuring a target (detecting an analyte) (Abstract). Kawabata et al. teaches a target substance (analyte) is reacted with an affinity molecule forming a complex (p. 1 paragraph 0008). Kawabata et al. teaches the separation of the complex from nucleic acid chain-binding affinity substances not involved in the formation of the complex (separation of the complex and unbound affinity

molecule) (p. 13 paragraph 73). Kawabata et al. teaches adding heparin (charged polymer) to the solution of nucleic acid chain-binding affinity substances in the separation method (p. 23 paragraphs 144-145). Kawabata et al. teaches separating the complex using capillary electrophoresis with a channel diameter preferably 1 to 200 microns (p. 12 paragraph 58). Kawabata et al. teaches a method for measuring (detecting) a target separated by complexing with a nucleic acid chain-binding affinity substance (abstract). Krylov et al. teaches immobilizing heparin on the capillary wall of the separation chamber (p. 122R 2nd column 1st full paragraph).

Therefore Kawabata et al. and Krylov et al. teaches a charged polymer in a separation media because Krylov et al. teaches immobilizing heparin to the capillary wall of the separation chamber, however, Kawabata et al. and Krylov et al. do not teach the concentration of the charged polymer (heparin) in a separation media.

With regard to Claim 34 and 91, Stalcup et al. teaches using 2% heparin in the phosphate buffer in capillary zone electrophoresis (abstract).

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the capillary electrophoresis method of Kawabata et al. and Krylove et al. to include 2% concentration or charged polymers in a buffer as taught by Stalcup et al. The ordinary artisan would have been motivated to modify the capillary electrophoresis method of Kawabata et al. and Krylove et al. to include 2% concentration or charged polymers in a buffer as taught by Stalcup et al., because Stalcup et al. teaches the highly anionic character of heparin enhances its aqueous solubility while offering the potential for considerable electrophoretic mobility

and therefore has utility as a chiral mobile phase additive in capillary zone electrophoresis (p. 3054 1st column 2nd paragraph).

Response to Arguments

The reply traverses the rejection. The reply asserts the art presented in the rejection do not teach a separation channel in a microfluidic device filled with separation media and a charged polymer. This argument has been thoroughly considered but has not been found persuasive. As discussed above in the rejection of Kawabata et al. and Krylov et al. the arguments and amendments have not overcome the art of record.

12. Claim 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kawabata et al. (EP 1376126A1 3/04/2002) as evidenced by Walston et al. (US Patent Application Publication 2001/0055591 December 27, 2001) in view of Krylov et al. (Anal Chem 2000 Vol. 72 p. 111R) as applied to Claims 1-3, 6, 9-29, 33, 35-44, 51-55, 59-65, 67, 68-78, 81, 83, 85-86, 90, and 92-100 in the rejection above in further view of Fukui et al. (Nucleic acid Research, 1996 Vol. 24 p. 3962).

Kawabata et al. teaches a method of measuring a target (detecting an analyte) (Abstract). Kawabata et al. teaches a target substance (analyte) is reacted with an affinity molecule forming a complex (p. 1 paragraph 0008). Kawabata et al. teaches the separation of the complex from nucleic acid chain-binding affinity substances not involved in the formation of the complex (separation of the complex and unbound affinity molecule) (p. 13 paragraph 73). Kawabata et al. teaches adding heparin (charged

polymer) to the solution of nucleic acid chain-binding affinity substances in the separation method (p. 23 paragraphs 144-145). Kawabata et al. teaches separating the complex using capillary electrophoresis with a channel diameter preferably 1 to 200 microns (p. 12 paragraph 58). Kawabata et al. teaches a method for measuring (detecting) a target separated by complexing with a nucleic acid chain-binding affinity substance (abstract). Krylov et al. teaches immobilizing heparin on the capillary wall of the separation chamber (p. 122R 2nd column 1st full paragraph).

Kawabata et al. teaches the charged carrier is a nucleic acid chain (nucleotide chain, DNA) (p. 3-4 paragraph 6). Kawabata et al. teaches the nucleic acid chain used may be prepared by chemical synthesis (synthetic) (p. 6 paragraph 15).

Therefore Kawabata et al. and Krylov et al. teach synthetic sequences, however, do not teach a synthetic sequence consisting of a nucleotide that contains a methylene group in the place of the oxygen in the ribose ring.

Fukui et al. teaches linking ACMA to DNA (abstract). With regard to Claim 66, Fukui et al. teaches the ACMA is connecter through a tri-pentamethylene linker (Abstract). Therefore, Fukui et al. teaches a synthetic sequence consisting of a linker, which has a methylene group.

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the capillary electrophoresis method comprising synthetic sequences with one or more linker groups of Kawabata et al. and Krylove et al. to include the specific methylene linker as taught by Fukui et al. The ordinary artisan would have been motivated to modify the capillary electrophoresis method of Kawabata

et al. and Krylove et al. to include methylene linker as taught by Fukui et al., because Fukui et al. teaches a pentamethylene linker which stabilizes the connection between ACMA and the DNA (Abstract) can be used to attach labeling constants to the DNA.

Response to Arguments

The reply traverses the rejection. The reply asserts the art presented in the rejection do not teach a separation channel in a microfluidic device filled with separation media and a charged polymer. This argument has been thoroughly considered but has not been found persuasive. As discussed above in the rejection of Kawabata et al. and Krylov et al. the arguments and amendments have not overcome the art of record.

13. Claims 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawabata et al. (EP 1376126A1 3/04/2002) as evidenced by Walston et al. (US Patent Application Publication 2001/0055591 December 27, 2001) in view of Krylov et al. (Anal Chem 2000 Vol. 72 p. 111R) as applied to Claims 1-3, 6, 9-29, 33, 35-44, 51-55, 59-65, 67, 68-78, 81, 83, 85-86, 90, and 92-100 in the rejection above in further view of Kaniansky et al. (Analytical chemistry 2000 Vol. 72 p. 3596).

Kawabata et al. teaches contacting a sample, with an affinity attached to a nucleic acid chain, which is labeled (Figure 2). Kawabata et al. teaches separating the complex using capillary electrophoresis (p. 12 paragraph 58). Kawabata et al. teaches a method of capillary chip electrophoresis comprising adding a buffer and sample to a sample reservoir, applying voltage and migrating the sample through a capillary wherein

the sample which goes completely through the first capillary is introduced into a capillary for separation (p. 12 paragraph 56 and Figure 7). For the first capillary, the sample is concentrated because only the sample that goes through the entire first capillary is introduced into the capillary for separation, therefore, the first capillary is a concentration channel. Kawabata et al. teaches the capillary used is 100 micron or less (p. 11-12 paragraph 54). Kawabata et al. teaches a nucleic acid chain (charge carrier molecule) attached to an affinity substance attached to a target (analyte) (Figure2). Kawabata et al. teaches the addition of the charged substance improves separation ability (p. 2-3 paragraph 9). Krylov et al. teaches immobilizing heparin on the capillary wall of the separation chamber (p. 122R 2nd column 1st full paragraph).

Therefore, Kawabata et al. and Krylove et al. teach concentrating the analyte, however, do not teach the concentration using isotachophoresis (ITP).

With regard to Claims 57-58, Kaniansky et al. teaches a method of using a capillary electrophoresis chip with a two separation channel coupling (Abstract). Kaniansky et al. teaches using ITP as a concentration pretreatment of the analyte (Abstract).

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the capillary electrophoresis method of Kawabata et al. to include the ITP concentration method as taught by Kaniansky et al. The ordinary artisan would have been motivated to modify the capillary electrophoresis method of Kawabata et al. to include the ITP concentration method as taught by Kaniansky et al. because Kaniansky et al. teaches using an ITP concentration

pretreatment quantified test analytes by 1-2% RSD (Abstract). Kaniansky et al. teaches a well-defined ITP concentration of the analyte can be integrated into the separation method of a capillary channel chip (Abstract).

Response to Arguments

The reply traverses the rejection. The reply asserts the art presented in the rejection do not teach a separation channel in a microfluidic device filled with separation media and a charged polymer. This argument has been thoroughly considered but has not been found persuasive. As discussed above in the rejection of Kawabata et al. and Krylov et al. the arguments and amendments have not overcome the art of record.

14. Claims 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawabata et al. (EP 1376126A1 3/04/2002) as evidenced by Walston et al. (US Patent Application Publication 2001/0055591 December 27, 2001) in view of Krylov et al. (Anal Chem 2000 Vol. 72 p. 111R) as applied to Claims 1-3, 6, 9-29, 33, 35-44, 51-55, 59-65, 67, 68-78, 81, 83, 85-86, 90, and 92-100 in the rejection above in further view of Wolfe et al. (Electrophoresis March 23, 2002 Vol. 23 p. 727).

Kawabata et al. teaches contacting a sample, with an affinity attached to a nucleic acid chain, which is labeled (Figure 2). Kawabata et al. teaches separating the complex using capillary electrophoresis (p. 12 paragraph 58). Kawabata et al. teaches a method of capillary chip electrophoresis comprising adding a buffer and sample to a sample reservoir, applying voltage and migrating the sample through a capillary wherein

the sample which goes completely through the first capillary is introduced into a capillary for separation (p. 12 paragraph 56 and Figure 7). For the first capillary, the sample is concentrated because only the sample that goes through the entire first capillary is introduced into the capillary for separation, therefore, the first capillary is a concentration channel. Kawabata et al. teaches the capillary used is 100 micron or less (p. 11-12 paragraph 54). Kawabata et al. teaches a nucleic acid chain (charge carrier molecule) attached to an affinity substance attached to a target (analyte) (Figure2). Kawabata et al. teaches the addition of the charged substance improves separation ability (p. 2-3 paragraph 9). Krylov et al. teaches immobilizing heparin on the capillary wall of the separation chamber (p. 122R 2nd column 1st full paragraph).

Therefore, Kawabata et al. and Krylove et al. teach concentrating the analyte, however, do not teach that the concentration based on adsorption of the charged carrier.

With regard to Claims 56-57, Wolfe et al. teaches the incorporation of a silica-based solid phase extraction (SPE) system into a microchip platform (the same platform described by Kawabata et al) (Abstract). Wolfe et al. teaches the extraction procedure utilizes the adsorption of DNA onto bare silica (abstract). Wolfe et al. teaches that DNA is removed from the sample load solution and is retained in the washing step (p. 732 1st column last paragraph). Therefore DNA is adsorbed while "noise constituents" are washed away.

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the capillary electrophoresis method of

Kawabata et al. and Krylove et al. to include the SPE concentration method as taught by Wolfe et al. The ordinary artisan would have been motivated to modify the capillary electrophoresis method of Kawabata et al. and Krylove et al. to include the SPE concentration method as taught by Wolfe et al. because Wolfe et al. teaches a method of concentrating DNA (so therefore the charged carrier attached to the affinity molecule and the analyte) from noise constituents in the sample by adhering the DNA onto a silica wall (Abstract). The ordinary artisan would be motivated to use the SPE concentration method because Wolfe et al. teaches the extraction of nanogram quantities of DNA in less than 25 minutes (abstract). The ordinary artisan would be motivated to concentrate the charge carrier, affinity, and analyte from noise constituents in a fast and efficient manner.

Response to Arguments

The reply traverses the rejection. The reply asserts the art presented in the rejection do not teach a separation channel in a microfluidic device filled with separation media and a charged polymer. This argument has been thoroughly considered but has not been found persuasive. As discussed above in the rejection of Kawabata et al. and Krylov et al. the arguments and amendments have not overcome the art of record.

Conclusion

15. No Claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

/Jehanne Sitton/

Primary Examiner

9/27/2007